REMARKS

Claims 4, 7-10, 17-22, and 60-80 are pending in this application. Applicants have amended claims 4, 7-9, 17, 18, 20, 62, 64, and 65, and canceled withdrawn claims 23-59 without prejudice or disclaimer. Claims 66-80 are new. Support for the new claims can be found in the application as filed, for example, in previously-pending claims 64 and 65, and the specification as filed, e.g., paragraphs 50-60 at pages 13-16. Support for the amendment to claims 4 and 7-9 can be found in the application as filed, e.g., at page 58, lines 1-5 and page 59, lines 17-19, and merely clarifies that the polyarginine recited in the claims is a separate element. No new matter has been added.

Withdrawn Rejections

Applicants thank the Examiner for withdrawing the 35 U.S.C. § 112 Enablement and Written Description rejections from the previous Office Action.

Claim Objections

Claim 62. The Office objects to claim 62 for the recitation of "with." to end the claim. Applicants have amended claim to recite "with polyarginine." and submit that the amendment overcomes the objection.

Claims 64 and 65. The Office objects to claims 64 and 65 for being multiply dependent claims that depend from multiply dependent claims. Applicants have amended claims 64 and 65 to each depend from claim 4 only. New claims have been added to recite the canceled subject matter.

The Office further objects to claim 64 for punctuation. Applicants submit that the amendment to claim 64 obviates this objection.

Double Patenting Rejection

At pages 3-4, the Office provisionally rejects claim 4 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 4, 7, 9, and 10 of co-pending application no. 11/169,956.

Because neither application has issued as a patent and no conflicting claims have thus been patented, Applicants respectfully defer addressing this rejection (MPEP § 804(I)).

35 U.S.C. §102

The Office at pages 4-5 of the Office Action alleges that claims 4, 7-10, 17, 19, 22, and 60-65 are anticipated by Sorensen et al. (US Pat. No. 5,849,700; "Sorensen"). Specifically, the Office alleges that:

> Sorensen et al. teach a crystal of human growth hormone (hGH) in Example 4 which consists of the 191 amino acid sequence because "Human growth hormone consists of 191 amino acids." As shown in the hGH sequence, the sequence of hGH contains many arginine residues and meets the limitation of a polyarginine containing crystal of hGH. Thus, the hGH crystal of Sorensen et al. meets the limitations of Claim 4. (Office Action at page 4; internal citations omitted)

Applicants respectfully disagree with the Office's position. Applicants have amended claims 4 and 7-9 to clarify that the polyarginine recited in the claims does not refer to arginine residues that may be present in the hGH protein. Rather, as the amended claims clearly indicate, polyarginine, a polyamino acid, is a separate element of the claims. As indicated above, the application as filed describes crystals that contain an excipient, e.g., a polyamino acid (such as polyarginine), and hGH. As stated on page 19, lines 17-28:

> [0066] In another aspect of the invention, the pharmaceutically acceptable excipient is selected from the group consisting of polyamino acids, including polylysine, polyarginine and polyglutamate. In a preferred embodiment of this invention, the excipient is polylysine. In a more preferred embodiment, polylysine has a molecular weight between about 1,500 and about 8,000 kD. In another embodiment, the crystals of hGH or an hGH derivative and polylysine are present in an hGH:polylysine ratio of about 5:1 to about 40:1 (w/w). That ratio may also range between about 10:1 to about 20:1 (w/w). Most preferably, that ratio ranges between about 12:1 to about 15:1 (w/w). According to an alternate embodiment, that ratio is about 5:1 to about 1:50 (w/w). And, in a further embodiment, that ratio is about 5:1 (w/w).

As another example, page 27, line 24 to page 28, line 15 teach:

> [0084] According to one embodiment, compositions comprising crystals of hGH or an hGH derivative according to the present invention are characterized by an hGH concentration greater than about 0.1 mg/ml. For example, that concentration may be between about 0.1 mg/ml and about 100 mg/ml. Alternatively, those compositions may be characterized by an hGH concentration between about 1 mg/ml and about 100 mg/ml or between about 10 mg/ml and about 100 mg/ml. Such compositions also include the following components: mannitol--about 0.5 mg/ml to about 100 mg/ml; sodium acetate--about 5 mM to about 250 mM (preferably about 25 mM to about 150 mM; Tris HCl--about 5 mM to about 100 mM; pH about 6.0 to about 9.0 (preferably about 6.5 to about 8.5);

> PEG (MW 800-8000, preferably 3350, 4000, 6000 or 8000)-0 to about 25%; protamine, preferably a 3:1 ratio of hGH: protamine; and polyarginine, preferably a 5:1 ratio of hGH: polyarginine. Such compositions may optionally comprise: sucrose--0 mg/ml to about 100 mg/ml; amino acids (e.g., arginine and glycine)--0 mg/ml to about 50 mg/ml; preservatives (antimicrobial, phenol, metacrescol, benzyl alcohol, parabenzoate (paraben))--0% to about 5% (preferably 0% to about 0.9%); and polysorbate--0 mg/ml to about 10 mg/ml. According to one embodiment, compositions according to this invention are characterized by 80% effective loading.
>
> [0085] A preferred formulation vehicle according to the present invention comprises about 100 mM sodium acetate, about 5% PEG 6000 MW and about 25 mM Tris.HCl, pH 7.5. An hGH composition prepared using such a vehicle may comprise: about 9.35 mg/ml crystalline hGH and about 1.81 mg/ml polyarginine (or about 3.12 mg/ml protamine). As will be appreciated by those of skill in the art, given that compositions according to this invention may comprise about 1 mg/ml to about 100 mg/ml hGH concentration, the polyarginine (or protamine) concentration should be adjusted accordingly, so that it is sufficient to maintain a 5:1 rhGH:polyarginine (w/w) ratio or a 3:1 hGH:protamine (w/w) ratio and maintain low solubility and release of hGH of about 5 ng/ml. For example, for the above-described formulation, if the desired crystalline hGH concentration is about 20 mg/ml, the polyarginine (or protamine) concentration should be about 4 mg/ml.

Further, the application as filed provides examples of crystals that contain polyarginine and hGH (see, e.g., page 58, lines 1-22 and page 59, line 17 to page 60, line 24). Thus, the polyarginine recited in the claims is an element distinct from the hGH recited therein.

Sorensen describes the preparation of hGH compositions, such as crystals, that contain histidine or a derivative thereof (see, e.g., col. 1, lines 11-14 of Sorensen). It fails to teach, or even suggest, crystals that contain polyarginine and hGH. For at least this reason, Sorensen does not anticipate claims 4, 7-10, 17, 19, 22, or 60-65.

The Office at page 5 of the Office Action alleges that the properties recited in claims 7-9 and 10 are inherently present in Sorensen, stating:

> The hGH crystal of Sorensen et al. is considered to have the said characteristics of claims 7-9 as evidenced by the instant disclosure of pharmacokinetic parameters in applicants' Table 6, in Example 16, on page 54-56. Those recited limitations after the "wherein the crystal" do not appear to be associated with a particular structure or component of the claimed crystal and have been considered accordingly. Said "limitations" are considered inherent characteristics of the crystal of Sorensen et al. based upon the structure of the crystal. This is evidenced because claimed crystal is of human growth hormone, and based on the rat model as shown in Example 16, the crystal would have the same characteristics when said crystal is administered to a human. Thus, the crystal of Sorensen et al. meets the limitation of claim 10.

Applicants disagree with this allegation. As indicated at page 54, lines 4-5, the results shown in Example 16 were obtained with the hGH crystals from Example 10. The crystals from Example 10 contain calcium acetate and 2% polyethylene glycol (PEG-6000), which are <u>not</u>

present in the crystals prepared by Sorensen. Thus, no extrapolation of the results shown in Applicants' Example 16 can be made to the crystals of Sorensen, as the two crystals are not the same. Further, claims 7-9 and 10 recite crystals that contain polyarginine and hGH. Such crystals are not disclosed in Sorensen. For at least these reasons, Applicants respectfully request that this rejection be withdrawn.

The Office goes on to state, "Sorensen et al. also teach a composition comprising said crystal (1.3 mg/ml) with Benzyl alcohol in Example 7, column 17; thus meeting the limitation of Claims 17, 19 and 22" (Office Action at page 5).

Applicants respectfully disagree. Each of claims 17, 19, and 22 depend from claims 4, 7, 8, and 9, which recite crystals that contain polyarginine and hGH. Such crystals are not disclosed in Sorensen. For at least this reason, Applicants respectfully request that this rejection be withdrawn.

With respect to claims 60-63 and 65, the Office alleges, "The crystal of Sorensen et al. also meets the limitation of Claims 60-63 and 65 because recited 'the polyarginine containing crystal' of hGH reads on a multiple arginine residues in hGH crystal" (*Id.*).

Applicants respectfully disagree. Claims 60-63 and 65 depend from claims 4, 7, 8, and/or 9, which recite crystals that contain polyarginine and hGH. Such crystals are not disclosed in Sorensen. For at least this reason, Applicants respectfully request that this rejection be withdrawn.

The Office further alleges that, "Sorensen et al. also teach a pharmaceutical composition of said hGH crystal with sodium cation in the Example 9, column 17; thus meeting the limitation of Claim 64" " (*Id.*).

Applicants respectfully disagree. Claim 64 depends from claim 4, which recites crystals that contain polyarginine and hGH. Such crystals are not disclosed in Sorensen. For at least this reason, Applicants respectfully request that this rejection be withdrawn.

Because Sorensen fails to anticipate the subject matter of claims 4, 7-10, 17, 19, 22, and 60-65, Applicants respectfully request that this rejection be withdrawn.

35 U.S.C. §103

The Office at pages 5-8 alleges that claims 4, 7-10, 17-22, and 60-65 are obvious in light of Sorensen and DeFelippis et al. (*J. Pharm. Sci.* 87:170176 (1998); "DeFelippis"). Applicants respectfully disagree.

The Office Action at page 7 indicates that DeFelippis is being relied on solely for its descriptions of an excipient and a molar ratio of hGH:excipient.

Claims 4 and 7-9 have been amended to clarify that the crystals recited therein contain polyarginine and hGH. As discussed above, nothing in Sorensen teaches or suggests this subject matter. DeFelippis does not make up for the deficiencies of Sorensen. The disclosure in DeFelippis pertains to the crystallization of an insulin analogue. DeFelippis offers no teaching or suggestion regarding hGH crystals, or crystals that contain polyarginine and hGH.

Thus, because nothing in Sorensen or DeFelippis, alone or in combination, teaches or suggests the claimed subject matter, claims 4, 7-10, 17-22, and 60-65 are non-obvious in light of Sorensen and DeFelippis. For at least these reasons, withdrawal of this rejection is respectfully requested.

CONCLUSION

For at least the reasons stated above, Applicants respectfully submit that all pending claims are in condition for allowance, which action is expeditiously requested. Applicants do not concede any positions of the Examiner that are not expressly addressed above, nor do Applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

This supplemental Amendment is being filed in response to the Notice of Non-Compliant Amendment mailed September 30, 2008 and the Office Action mailed December 26, 2007. No fees are believed to be due. If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. Please charge any deficiency to Deposit Account No. 50/2762.

Respectfully submitted,
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